REMARKS

The United States Patent and Trademark Office has issued two Office Actions, one dated January 6, 2004 and the second one dated February 13, 2004. As the Office Action has indicated and with which applicant agrees, the second Office Action did not raise any new issues therein. It appears to have been issued as a result of the Preliminary Amendment dated January 5, 2004 filed by applicant, i.e., a date prior to the issuance of either Office Action. Thus, a response to the issues raised in the First Official Action will also respond to the issues in the Second Official Action. Thus, when responding to the issues in the two Official Actions, applicants will refer to the Official Action dated January 6, 2004, which is referred to herein as the "first Official Action".

The first Official Action has rejected Claim 1 under 35 U.S.C. §102(a) as defining subject matter which is allegedly anticipated by the teachings in U.S. Patent No. 4,707,468 to Yoshino, et al. ("Yoshino, et al."). In addition, Claim 1 is rejected under 35 U.S.C. §102(b) as allegedly anticipated by the teachings in WO 99/143309 ("Bialer, et al."). It is to be noted that the Official Action only rejects Claim 1; it has only objected to the remaining claims, namely, Claims 2-19, 51, 56-62 and 73-74.

Applicant submits that the following Amendment, which, when considered with the comments hereinbelow places the present case in condition for allowance. Favorable action is respectfully requested.

Before addressing the merits, it is to be noted that applicant has amended the claims and added claims to the application. Applicant has amended Claim 1, et seq. More specifically, as amended, R_3 is not hydrogen and n is 1. Applicant has amended the claims to emphasize the subject matter which is preferred.

Support for these amendments is found in the instant specification. For example, support for "n being 1" is found on Page 25, line 20 of the instant application.

Further, as amended, R^2 and R^3 are amended to include aryl. Support is found on Page 16, line 1 to Page 17, lien 28, especially on Page 10, lines 25-31. R_3, is defined as being other than hydrogen. Support is found in the instant specification. For example, as defined on Page 15, line 27 to Page 17, line 34 of the instant specification R_2 and R_3 are independently members of the Markush grouping defined as being selected from the group consisting of hydrogen, lower alkyl, lower alkyl lower alkynyl, aryl, aryl lower alkyl halo, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic lower cycloalkyl, lower cycloalkyl, lower alkyl or ZY, and R_2 and R_3 may be unsubstituted or substituted. Thus, R_2 as defined originally contained each of the above-identified members of the Markush grouping and so did R_3. In the amendment, applicant has deleted one of the terms from the definition of R_3. Further, attention is directed to Claim 2 as originally filed, which states that one or R_2 and R_3 is hydrogen; this means that the other is not hydrogen. Thus, there is support in the application for one of R_2 and R_3 being other than hydrogen. It is to be noted that there is no stereochemistry depicted in Formula I as drawn, therefore R_2 is equivalent to R_3. Consequently, it is arbitrary which one of R_2 and R_3 is defined to be other than hydrogen. Thus, applicant has amended the claims so that R_3 excludes hydrogen from its definition. Claim 51 has been amended to recite the electron donating groups and the electron withdrawing groups as described on Page 20, lines 7-31 of the instant specification.

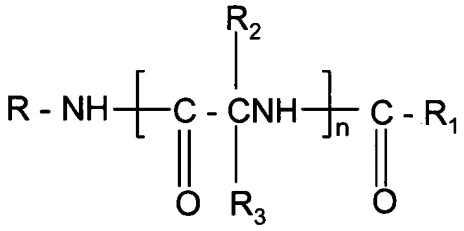
The remaining pending claims have been amended to be consistent therewith.

Applicant has also added Claims 75-89 to the application. Support for Claims 75 and 76 are found on Page 25, lines 31-32 of the present specification, while support for Claims 77 and 78 are found on Page 26, lines11-12 of the specification. Further, support for Claim 79 is found on Page

25, lines 16-19, Claim 2,Page 25, lines 31-32 and Page 26, lines 11-12 of the instant specification. Support for Claims 80-81 is found on Page 26, line 12 to page 27, line 15 of the instant specification. In addition, support for Claim 82 is found on Page 20, lines 7-31 of he instant application. Finally, support for Claims 83-89 is found on Page 24, line 29 to Page 27, line 10 of the instant application.

No new mater is added to the application.

The present invention, as amended, is inter alia, directed to a method for alleviating pain in a patient suffering therefrom comprising administering to said patient an analgesic effective amount of a compound of the formula:



wherein

R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group or electron donating group;

R_1 is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower alkyl heterocyclic, lower cycloalkyl, lower, cycloalkyl lower alkyl, each unsubstituted or substituted with an electron donating group or an electron withdrawing group; and

R_2 is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, halo, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, or Z-Y;

R_3 is independently lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, lower alkyl, heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl or Z-Y;

wherein R_2 and R_3 may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group wherein the electron donating group or electron withdrawing group is acyclic; and wherein heterocyclic in R_2 and R_3 is furyl, thienyl, pyrazolyl, pyrrolyl, imidazolyl, indolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, piperidyl, pyrrolinyl, piperazinyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, benzofuryl, benzothienyl, morpholinyl, benzoxazolyl, tetrahydrofuryl, pyranyl, indazolyl, purinyl, indolinyl, pyrazolindinyl, imidazolinyl, imidazolindinyl, pyrrolidinyl, furazanyl, N-methylindolyl, methylfuryl, pyridazinyl, pyrimidinyl, pyrazinyl, epoxy, aziridino, oxetanyl or azetidinyl;

Z is O, S, $S(O)_a$, NR_6', or PR_4;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, heterocyclic, heterocyclic lower alkyl, and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, or

ZY taken together is $NR_4NR_5R_7$, NR_4OR_5, ONR_4R_7, OPR_4R_5, PR_4OR_5, SNR_4R_7, NR_4SR_7, SPR_4R_5, PR_4SR_7, $NR_4PR_5R_6$, $PR_4NR_5R_7$,

$NR_4C(=O)-R_5$, SCR_5, $NR_4C(=O)-OR_5$, or $SC(=O)-OR_5$;

R_6' is hydrogen, lower alkyl, lower alkenyl, or lower alkynyl and R_6' may be unsubstituted or substituted with an electron withdrawing group or electron donating group;

R_4, R_5 and R_6 are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein R_4, R_5 and R_6 may be unsubstituted or substituted with an electron withdrawing group or an electron donating group; and

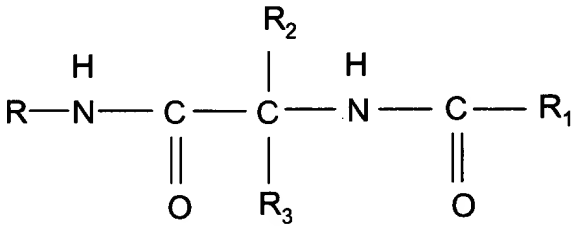
R_7 is $COOR_8$, COR_8, hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl or lower alkynyl, which R_7 may be unsubstituted or substituted with an electron withdrawing group or electron donating group;

R_8 is hydrogen or lower alkyl, or aryl lower alkyl, and the aryl or alkyl group may be unsubstituted or substituted with an electron withdrawing group or an electron donating group; and

n is 1; and

a is 1-3.

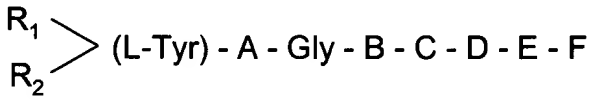
Thus, as amended, the compound of Formula I utilized has the formula



I

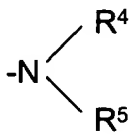
Thus, the compounds of Formula I contains only two amide linkages in the main chain. Moreover, as amended R_2 and R_3 cannot both be hydrogen. In fact, as amended, R_3 is not hydrogen.

In support of the first rejection of Claim 1 under 35 U.S.C. §102(b), the Office Action cites Yoshino, et al. Yoshino, et al. disclose a polypeptide of the formula

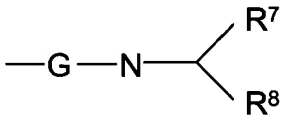


wherein R^1 and R^2 may be the same or different and each represents a hydrogen atom or a lower alkyl or lower alkenyl group, A represents a D-amino acid, Gly or Sar provided that when the D-amino acid is D-Cys, it is bonded with L-Cys or D-Cys in position 5 through a S-S bond to effect intramolecular ring closure, B represents L-Phe or D-Phe in which the benzene ring may be

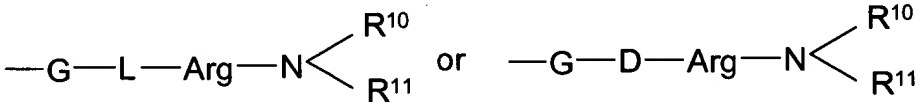
substituted or an α-N-alkyl derivative thereof, C represents an L-amino acid, D-Cys or an α-N-alkyl derivative thereof, D and E each represent an L- or D-basic amino acid or an α-N-alkyl derivative thereof, F represents a group of the formula $-OR^3$ (in which R^3 is H or a lower alkyl group), a group of the formula:



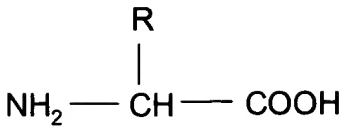
(in which R^4 and R^5 are the same or different and each represents H or a lower alkyl group), a group of the formula: $-G-OR^6$ (in which G is an L- or D-amino acid or Gly or an α-N-alkyl derivative thereof and R^6 represents H or a lower alkyl group), a group of the formula:



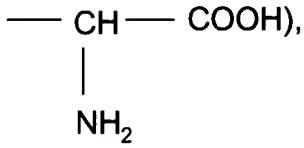
(in which G is as defined above and R^7 and R^8 may be the same or different and each represents H or a lower alkyl group), a group of the formula: $-G-L-Arg-OR^9$ or $-G-D-Arg-OR^9$ (in which G is as defined above and R^9 represents H or a lower alkyl group or a group of the formula:



(in which G is as defined above and R^{10} and R^{11} may be the same or different and each represents H or a lower alkyl group), a group of the formula: $-G-J-OR^{12}$ in which G is defined as above, J is a neutral amino acid group or an acidic amino acid group and R^{12} is hydrogen or a lower alkyl group; or a group of the formula: $-G-Arg-M-OR^{13}$ in which M is D-amino acid group and R^{13} is hydrogen or a lower alkyl group, provided that all of the amino acids constituting the polypeptide of the above formula do not represent at the same time an L-amino acid of the general formula:



(in which R represents a group corresponding to a structural formula of an amino acid deprived of a group of the formula:



or pharmacologically acceptable salts of them. It is alleged that the polypeptides therein have analgenic properties.

In Yoshino, et al., the compounds that have utility for treating pain have several peptide linkages, for example, one between Tyr and A, another between A and Gly, between Gly and B, between B and C, between C and D, and between D and E.

Moreover, the examples referred to in the Office Action has the

Me-Tyr-Gly-Gly-Phe-Leu-Arg-Arg-NH

Thus, as defined, the compounds in Yoshino contain at least 6 peptide linkages. It does not disclose any compounds therein having 2 amide linkages (C-NH)

in the main chain for treating pain. On the other hand, as amended, the compounds used in the present invention contain only 2 amide linkages in the main chain.

Anticipation requires identity of invention; a finding of anticipation requires that the publication described all of the elements of the claims. See, for example, Continental Can Co., USA., Inc. v. Monsanto Co., 948 F2d. 1264, 1267, 20 USPQ2d 1746, 1748 (Fed. Cir. 1991); In re Spada, 911 F2d. 705, 708, 15 USPQ2d. 1655, 1657 (Fed. Cir. 1990).

Inasmuch as Yoshino, et al. do not disclose any compounds therein for treating pain having only 2 amide linkage in the main chain, it does not teach, disclose or suggest the use of the compounds of the present invention. Therefore, the rejection of Claim 1 is obviated; withdrawal thereof is respectfully requested.

In support of the rejection of Claim 1, the United States Patent and Trademark Office also alleges that Bialer, et al. disclose the present invention. More specifically, it refers to Claim 16 thereof.

Claim 16 refers to a pharmaceutical composition for treating pain wherein the active ingredient may be N-acetyl-N'-benzylglycinamide. According to the Office Action, the claim is anticipated when n is 1, R_1 is methyl and R is benzyl and both R_2 and R_3 are hydrogen. However, as amended, R_3 cannot be hydrogen. Thus, the present invention does not include the use of compound when n is 1, R_1 is methyl, R is benzyl and both R_2 and R_3 are hydrogen. Thus, as amended, the subject matter of the prior art does not anticipate the subject matter of Claim 1. Therefore, the rejection of Claim 1 under 35 U.S.C. §102(b) as being anticipated by Bialer, et al. is overcome; withdrawal thereof is respectfully requested.

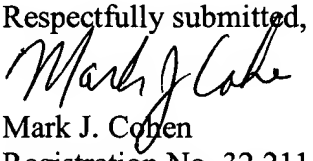
Since applicant has overcome the two rejections of Claim 1, the remaining claims are no longer dependent upon a rejected base claim. Therefore, the objections to the pending claims is overcome; withdrawal thereof is respectfully requested.

On another matter, applicant notes that the United States Patent and Trademark Office has not considered the article to Fu, et al. in the Journal of Pharmacology and Experimental Therapeutics, 2000, 294, 458-465 listed in the Information Disclosure Statement filed on December 18, 2002 alleging that only the Abstract was provided. Applicant respectfully submits that the United States Patent and Trademark Office should have at least reviewed the Abstract and should have made

it of record. Nevertheless, in order to make the Information Disclosure Statement complete, applicants are enclosing a copy of the aforementioned article in a new Information Disclosure Statement. Consideration thereof is respectfully requested.

Thus, in view of the Amendments to the claims and the Remarks hereinabove, it is respectfully submitted that the present case is in condition for allowance which action is earnestly solicited.

Respectfully submitted,



Mark J. Cohen
Registration No. 32,211

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, NY 11530-0299
(516) 742-4343

MJC:lf